REMARKS

Claims 1 and 3-14 are pending in the present application.

Claims 1 and 3-7 provide a method for screening a substance which interacts with a specific region of a biomolecule having an activity, to regulate the activity, said biomolecule being selected from the group consisting of a protein, a nucleic acid and a sugar chain, said method comprising the following steps:

(a) a step of preparing a peptide library composed of a collection of recombinant organisms each presenting at least one of various peptides on its surface;

(b) a step of bringing the recombinant organisms of the peptide library into contact with the biomolecule;

(c) a step of selecting a recombinant organism that interacts with the biomolecule from the peptide library, with a proviso that the interaction is not an antigen-antibody reaction;

(d) a step of testing inhibitory effect of a substance, on an interaction between the selected recombinant organism and the biomolecule, wherein said substance is selected from a chemical compound library; and

(e) a step of selecting a substance inhibiting the interaction between the selected recombinant organism and the biomolecule, as the substance which interacts with the specific region of the biomolecule.

Claims 8-14 provide a method for screening a substance which interacts with a specific region of a biomolecule having an activity, to regulate the activity, said biomolecule being selected from the group consisting of a protein, a nucleic acid and a sugar chain, said method comprising the following steps:

(a) a step of constructing a peptide library composed of a collection of recombinant organisms each presenting at least one of various peptides on its surface;

(b) a step of bringing the recombinant organisms of the, peptide library into contact with the biomolecule;

(c) a step of selecting a recombinant organism that interacts with the biomolecule from the peptide library, with a proviso that the interaction is not an antigen-antibody reaction;

(d) a step of determining a peptide presented by the selected recombinant organism and preparing the peptide;

(e) a step of testing inhibitory effect of a substance, on an interaction between the peptide and the biomolecule, wherein said substance is selected from a chemical compound library; and

(f) a step of selecting a substance inhibiting the interaction between the peptide and the biomolecule, as the substance which interacts with the specific region of the biomolecule.

Applicants submit that none of the art of record discloses or suggests either of these methods provided by the present invention. As such, the art of record cannot affect the patentability of the present invention.

The rejection of Claims 1-3 and 5-6 under 35 U.S.C. §102(b), and alternatively under 35 U.S.C. §103(a), over Martens et al is obviated by amendment.

The Examiner cites Martens et al and asserts that this reference discloses a method of selecting inhibitory substances of E-selectin by using recombinant peptide display to screen for ligands that bind to E-selectin. The Examiner then asserts that Martens et al provides for

the selection of the highest affinity peptide, which is then determined for its inhibitory effect against a ligand binding to E-selectin.

Applicants note that Martens et al is silent with respect to steps (d) and (e) in amended Claim 1 and steps (d) – (f) in new Claim 8. More specifically, Martens et al fail to disclose or suggest a step of testing inhibitory effect of a substance, on an interaction between the selected recombinant organism and the biomolecule, wherein said substance is selected from a chemical compound library; and a step of selecting a substance inhibiting the interaction between the selected recombinant organism and the biomolecule, as the substance which interacts with the specific region of the biomolecule as required by Claim 1. Moreover, Martens et al fail to disclose or suggest a step of determining a peptide presented by the selected recombinant organism and preparing the peptide; a step of testing inhibitory effect of a substance, on an interaction between the peptide and the biomolecule, wherein said substance is selected from a chemical compound library; and a step of selecting a substance inhibiting the interaction between the peptide and the biomolecule, as the substance which interacts with the specific region of the biomolecule as required by Claim 8.

In view of the foregoing deficiencies in the disclosure of Martens et al, Applicants submit that Martens et al does not anticipate the present invention or render the present invention obvious. Withdrawal of these grounds of rejection is requested.

The rejection of Claims 1-6 under 35 U.S.C. §102(b), and alternatively under 35 U.S.C. §103(a), over O'Neill et al is obviated by amendment.

The Examiner cites O'Neill et al and asserts that this reference discloses a method for screening a substance inhibitor by selecting from a library of random peptides displayed on the surface of filamentous phage. The Examiner further asserts that O'Neill et al provides for

the selection and screening of peptides for inhibition of fibrinogen binding to platelets and inhibition of platelet aggregation.

Applicants note that O'Neill et al is silent with respect to steps (d) and (e) in amended Claim 1 and steps (d) – (f) in new Claim 8. More specifically, O'Neill et al fail to disclose or suggest a step of testing inhibitory effect of a substance, on an interaction between the selected recombinant organism and the biomolecule, wherein said substance is selected from a chemical compound library; and a step of selecting a substance inhibiting the interaction between the selected recombinant organism and the biomolecule, as the substance which interacts with the specific region of the biomolecule as required by Claim 1. Moreover, O'Neill et al fail to disclose or suggest a step of determining a peptide presented by the selected recombinant organism and preparing the peptide; a step of testing inhibitory effect of a substance, on an interaction between the peptide and the biomolecule, wherein said substance is selected from a chemical compound library; and a step of selecting a substance inhibiting the interaction between the peptide and the biomolecule, as the substance which interacts with the specific region of the biomolecule as required by Claim 8.

In view of the foregoing deficiencies in the disclosure of O'Neill et al, Applicants submit that O'Neill et al does not anticipate the present invention or render the present invention obvious. Withdrawal of these grounds of rejection is requested.

The rejection of Claims 1-6 under 35 U.S.C. §102(b), and alternatively under 35 U.S.C. §103(a), over Klein et al is traversed.

At the outset, Applicants would like to note that the disclosure of Klein et al is not available as art under 35 U.S.C. §102(b). Klein et al published on July 3, 2001 from an application filed on January 17, 1996, whereas the present application is the national stage of

an International PCT application, which has an effective U.S. filing date of March 10, 2000. Therefore, Klein et al is only available as art under 35 U.S.C. §102(e).

Klein et al disclose an assay using a library of recombinant cells, each cell of which include (i) a target receptor protein whose signal transduction activity can be modulated by interaction with an extracellular signal, the transduction activity being able to generate a detectable signal, and (ii) an expressible recombinant gene encoding an exogenous test polypeptide from a polypeptide library (column 2, lines 57-64).

In Klein et al, a yeast expression library in which the peptide is secreted from the yeast cell is used for identifying G protein coupled receptor effectors. Therefore, the interaction of the peptide and the receptor must be detected based on an *extracellular* signal, which arises from the receptor (for example, see column 8, lines 33-40). As is clearly evident from the disclosure of Klein et al, this measurement of the signal is often difficult. Klein et al even recognizes this potential problem with their method and even describes that if the test polypeptide does not appear to induce the activity of the receptor protein a more complicated system should be used (column 8, lines 45-67).

In contrast, the present invention utilizes a peptide library composed of a collection of recombinant organisms each presenting at least one of various peptides on its surface, i.e., a peptide-presenting recombinant organism library. Because the peptide-presenting recombinant organism library is used, the interaction can be easily detected by physically detecting the peptide-presenting recombinant organism. By the method of the present invention, therefore, the substance that interacts with a specific region of a biomolecule having an activity can be selected without measuring an activity of which the measurement is often difficult, i.e., the detection method utilized by Klein et al.

Applicants remind the Examiner that the standard for determining anticipation

requires that the reference "must teach every element of the claim" (MPEP §2131). In addition, citing In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974), MPEP §2143.03 states: "To establish a prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." Therefore, the absence of any disclosure or suggestion by Klein et al of the use of peptide-presenting recombinant organism library and the advantages obtained thereby would necessarily make this reference fail the tests for anticipation and/or obviousness.

Based on the foregoing, Applicants request withdrawal of these grounds of rejection.

The rejection of Claims 1-6 under 35 U.S.C. §112, first paragraph (enablement), is obviated in part by amendment and traversed in part.

MPEP § 2164.01 states:

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

Applicants submit that contrary to the assertions made by the Examiner, with the present specification in hand, the skilled artisan would readily appreciate how to practice the present invention without undue experimentation.

The claims have been amended to define the biomolecule as being selected from a protein, a nucleic acid or a sugar chain. The biomolecule is reasonably expected to interact with a peptide. For example, the method for detecting an interaction between the biomolecule (a protein, a nucleic acid or a sugar chain) and a peptide-presenting phage library are known, as shown in the following references **submitted herewith**:

Annu. Rev. Biophys. Biomol. Struet., 27, 401-424 (1997),

Methods in Enzymology, 267, 129-149 (1996), and

J. Immunol., 157, 732738 (1996)).

As is readily apparent from these references, phage display, i.e. peptide presenting phage library, is commonly used for selection of the biomolecules. Further, in the references that the Examiner cites in the aforementioned references (Martens et al and O'Neil et al) E-selectin and GPIIb/IIIa are used, respectively, and clearly indicated that even the Examiner appreciates that the skilled artisan would appreciate the enablement of phage display and that the biomolecule interacts with a peptide.

Moreover, the peptide libraries composed of various organisms other than phages are known to be used like the phage library. As seen from copies of the **attached references**, for example, a peptide-presenting insect cell virus library (Biotechnology (N Y), 13, 1079-1084 (1995)), a peptide-presenting animal virus library (Nat. Biotechnol., 16, 951-954 (1998)) and a peptide-presenting yeast library (Nat. Biotechnol., 15, 553-557 (1997)) are known. A peptide-presenting *E. coli* library is also known; as described on page 13, lines 14-20 of the present specification. Several types of the libraries have been commercially available from, for example, Invitrogen. Furthermore, as described on page 416 of Annu. Rev. Biophys. Biomol. Struct., 27, 401-424 (1997), the peptide-presenting recombinant organism library is not limited to the random one.

The Examiner appears to base, in part, this ground of rejection on the absence of sufficient working examples. However, Applicants direct the Examiner's attention to MPEP §2164.02, which states:

> The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation.

Therefore, the absence of working examples presenting each and every permutation of the present invention, in and of itself, is not sufficient to support an enablement rejection, nor is the omission of a working example.

Based on the foregoing, Applicants submit that the present claims are fully enabled by the specification and the common knowledge available in the art and as such withdrawal of this ground of rejection is requested.

The rejection of Claims 1-6 under 35 U.S.C. §112, second paragraph, is obviated in part by amendment and traversed in part.

With respect to the criticisms set forth by the Examiner regarding Claim 1, Applicants have amended Claim 1 to provide the "omitted essential steps." In addition, Applicants have removed the alternative language, which the Examiner believed to be confusing. Accordingly, Claim 1 is now believed to be definite.

The Examiner has held Claim 4 to be indefinite due to the recitation of "random peptide-presenting *E. coli.*" At the outset, Applicants have amended Claim 4 to specify that the peptide library is a "random peptide-presenting *E. coli* library." Further, Applicants direct the Examiner's attention to page 13, lines 14-20 of the present specification, which clearly shows that the scope and meaning of this term would be readily appreciated by the skilled artisan. In fact, this section of the specification shows that the peptide-presenting *E. coli* library is known in the art and is commercially available from Invitrogen. Applicants remind the Examiner that MPEP §2164.05(a) states:

> The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public... The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date.

Therefore, in view of the general knowledge available in the art, Applicants submit that the objected to language is, in fact, definite. Applicants also note that new Claim 10 contains the same language as discussed above for Claim 4.

Finally, regarding the Examiner's objection to the alternative language in Claim 6, Applicants note that this language has been removed from Claim 6. Accordingly, this claim is now believed to be definite.

Applicants request withdrawal of this ground of rejection.

The objection to the Abstract is believed to be obviated by the submission of the enclosed substitute Abstract. Acknowledgement that this ground of objection has been withdrawn is requested in the next action on the merits.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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